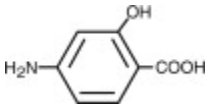
PASER - aminosalicylic acid granule, delayed release
Jacobus Pharmaceutical Company, Inc.

4 grams
Caution: Federal, law prohibits dispensing without prescription.
JACOBUS PHARMACEUTICAL COMPANY, INC.
Princeton, NJ 08540
2A JULY, 1996

PASER® GRANULES
(aminosalicylic acid granules)

DESCRIPTION

PASER granules are a delayed release granule preparation of aminosalicylic acid (p-aminosalicylic acid; 4-aminosalicylic acid) for use with other anti-tuberculosis drugs for the treatment of all forms of active tuberculosis due to susceptible strains of tubercle bacilli. The granules are designed for gradual release to avoid high peak levels not useful (and perhaps toxic) with bacteriostatic drugs. Aminosalicylic acid is rapidly degraded in acid media; the protective acid-resistant outer coating is rapidly dissolved in neutral media so a mildly acidic food such as orange, apple or tomato juice, yogurt or apple sauce should be used.
Aminosalicylic acid (p-aminosalicylic acid) is 4-Amino-2-hydroxybenzoic acid. PASER granules are the free base of aminosalicylic acid and do NOT contain sodium or a sugar. The molecular formula is $C_7H_7NO_3$ with a molecular weight of 153.14. With heat p-aminosalicylic acid is decarboxylated to produce CO_2 and m-aminophenol. If the airtight packets are swollen, storage has been improper. DO NOT USE if packets are swollen or the granules have lost their tan color and are dark brown or purple.
The structural formula is:



PASER granules are supplied as off-white tan colored granules with an average diameter of 1.5 mm and an average content of 60% aminosalicylic acid by weight. The acid resistant outer coating will be completely removed by a few minutes at a neutral pH. The inert ingredients are:

colloidal silicon dioxide

dibutyl sebacate

hydroxypropyl methyl cellulose

methacrylic acid copolymer

microcrystalline cellulose

talc

The packets contain 4 grams of aminosalicylic acid for oral administration three times a day by sprinkling on apple sauce or yogurt to be eaten without chewing. Suspension in an acidic fruit drink such as orange juice or tomato juice will protect the coating for at least 2 hours. Swirling the juice in the glass will help resuspend the granules if they sink.

CLINICAL PHARMACOLOGY

Mechanism of Action: Aminosalicylic acid is bacteriostatic against Mycobacterium tuberculosis. It inhibits the onset of bacterial resistance to streptomycin and isoniazid. The mechanism of action has been postulated to be inhibition of folic acid synthesis (but without potentiation with antifolic compounds) and/or inhibition of synthesis of the cell wall component, mycobactin, thus reducing iron uptake by M. tuberculosis.
Characteristics: The two major considerations in the clinical pharmacology of aminosalicylic acid are the prompt production of a toxic inactive metabolite under acid conditions and the short serum half life of one hour for the free drug. Both are discussed below.
After two hours in simulated gastric fluid, 10% of unprotected aminosalicylic acid is decarboxylated to form meta-aminophenol, a known hepatotoxin. The acid-resistant coating of the PASER granules protects against degradation in the stomach. The small granules are designed to escape the usual restriction on gastric emptying of large particles. Under neutral conditions such as are found in the small intestine or in neutral foods, the acid-resistant coating is dissolved within one minute. Care must be taken in the administration of these granules to protect the acid-resistant coating by maintaining the granules in an acidic food during dosage administration. Patients who have neutralized gastric acid with antacids will not need to protect the acid resistant coating with an acidic food since no acid is present to spoil the drug. Antacids may influence the absorption of other medications and are not necessary for PASER consumed with an acidic food.

Because PASER granules are protected by an enteric coating absorption does not commence until they leave the stomach; the soft skeletons of the granules remain and may be seen in the stool.

Absorption and excretion: In a single 4 gram pharmacokinetic study with food in normal volunteers the initial time to a 2μg/mL serum level of aminosalicylic acid was 2 hours with a range of 45 minutes to 24 hours; the median time to peak was 6 hours with a range of 1.5 to 24 hours; the mean peak level was 20 μg/mL with a range of 9 to 35 μg/mL; a level of 2 μg/mL was maintained for an average of 7.9 hours with a range of 5 to 9; a level of 1 μg/mL was maintained for an average of 8.8 hours with a range of 6 to 11.5 hours. The recommended schedule is 4 grams every 8 hours.

80% of aminosalicylic acid is excreted in the urine, with 50% or more of the dosage excreted in acetylated form. The acetylation process is not genetically determined as is the case for isoniazid. Aminosalicylic acid is excreted by glomerular filtration; although previously reported otherwise, probenecid, a tubular blocking agent, does not enhance plasma concentration. In a 1954 study thyroxine synthesis but not iodide uptake was reported reduced about 40% when the sodium salt (not PASER granules) of aminosalicylic acid was administered one hour before radio-iodine; the sodium salt typically produces a serum level over 120 μg/mL at one hour lasting one hour. Occasional goiter development can be prevented by the administration of thyroxine but not iodide.

Penetration into the cerebrospinal fluid occurs only if the meninges are inflamed.

Approximately 50-60% of aminosalicylic acid is protein bound; binding is reported to be reduced 50% in kwashiorkor.

Microbiology: The aminosalicylic acid MIC for M. tuberculosis in 7H11 agar was less than 1.0 μg/mL for nine strains including three multidrug resistant strains, but 4 and 8 μg/mL for two other multidrug resistant strains. The 90% inhibition in 7H12 broth (Bactec) showed little dose response but was interpreted as being less than or equal to 0.12-0.25 μg/mL for eight strains of which three were multi-resistant, 0.50 μg/mL for one resistant strain, questionable for four non-resistant strains and greater than 1μg/mL for one non-resistant and three resistant strains. Aminosalicylic acid is not active in vitro against M. avium.

INDICATIONS AND USAGE

PASER is indicated for the treatment of tuberculosis in combination with other active agents. It is most commonly used in patients with Multi-drug Resistant TB (MDR-TB) or in situations when therapy with isoniazid and rifampin is not possible due to a combination of resistance and/or intolerance. When PASER is added to the treatment regimen in patients proven or suspected drug resistance, it should be accompanied by at least one and preferably two other new agents to which the patient's organism is known or expected to be susceptible.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Severe renal disease.

Patients with severe renal disease will accumulate aminosalicylic acid and its acetyl metabolite but will continue to acetylate, thus leading exclusively to the inactive acetylated form; deacetylation, if any, is not significant.

The half life of free aminosalicylic acid in renal disease is 30.8 minutes in comparison to 26.4 minutes in normal volunteers. but the half life of the inactive metabolite is 309 minutes in uremic patients in comparison to 51 minutes in normal volunteers. Although aminosalicylic acid passes dialysis membranes, the frequency of dialysis usually is not comparable to the half-life of 50 minutes for the free acid. Patients with end stage renal disease should not receive aminosalicylic acid.

WARNINGS

Liver Function

In one retrospective study of 7492 patients on rapidly absorbed aminosalicylic acid preparations, drug-induced hepatitis occurred in 38 patients (0.5%); in these 38 the first symptom usually appeared within three months of the start of therapy with a rash as the most common event followed by fever and much less frequently by GI disturbances of anorexia, nausea or diarrhea. Only one patient was diagnosed on routine biochemistry.

Premonitory symptoms in 90% of these 38 patients preceded jaundice by a few days to several weeks with the mean time of onset 33 days with a range of 7-90 days. Half of the adverse reactions occurred during the third, fourth or fifth weeks. When aminosalicylic acid-induced hepatitis was diagnosed, hepatomegaly was invariably present with lymphadenopathy in 46%, leucocytosis in 79%, and eosinophilia in 55%. Prompt recognition with discontinuation led to the recovery of all 38 patients. If recognized in the premonitory stage, the reaction is reported to “settle” in 24 hours and no jaundice ensues. From other reported studies failure to recognize the reaction can result in a mortality of up to 21%. The patient must be monitored carefully during the first three months of therapy and treatment must be discontinued immediately at the first sign of a rash, fever or other premonitory signs of intolerance.

PRECAUTIONS

(1) General:

All drugs should be stopped at the first sign suggesting a hypersensitivity reaction. They may be restarted one at a time in very small but gradually increasing doses to determine whether the manifestations are drug-induced and, if so, which drug is responsible. Desensitization has been accomplished successfully in 15 of 17 patients starting with 10 mg aminosalicylic acid given as a single dose. The dosage is doubled every 2 days until reaching a total of 1 gram after which the dosage is divided to follow the regular

schedule of administration. If a mild temperature rise or skin reaction develops, the increment is to be dropped back one level or the progression held for one cycle. Reactions are rare after a total dosage of 1.5 grams.
Patients with hepatic disease may not tolerate aminosalicylic acid as well as normal patients, even though the metabolism in patients with hepatic disease has been reported to be comparable to that in normal volunteers.

(2) Information for Patients:
The patient should be advised that the first signs of hypersensitivity include a rash, often followed by fever, and much less frequently, GI disturbances of anorexia, nausea or diarrhea. If such symptoms develop, the patient should immediately cease taking the medication and arrange for a prompt clinical visit.
Patients should be advised that poor compliance in taking anti-TB medication often leads to treatment failure, and, not infrequently, to the development of resistance of the organisms in the individual patient.
Patients should be advised that the skeleton of the granules may be seen in the stool.
The coating to protect the PASER granules dissolves promptly under neutral conditions; the granules therefore should be administered by sprinkling on acidic foods such as apple sauce or yogurt or by suspension in a fruit drink which will protect the coating, but the granules sink and will have to be swirled. The coating will last at least 2 hours in either system. All juices tested to date have been satisfactory; tested are: tomato, orange, grapefruit, grape, cranberry, apple, “fruit punch”.
Patients should be advised to store PASER in a refrigerator or freezer. PASER packets may be stored at room temperature for short periods of time.
Patients should be advised NOT to use if the packets are swollen or the granules have lost their tan color and are dark brown or purple. The patient should inform the pharmacist or physician immediately and return the medication.

(3) Laboratory Tests:
Aminosalicylic acid has been reported to interfere technically with the serum determinations of albumin by dye-binding, SGOT by the azoene dye method and with qualitative urine tests for ketones, bilirubin, urobilinogen or porphobilinogen.

(4) Drug Interactions:
Aminosalicylic acid at a dosage of 12 grams in a rapidly available form has been reported to produce a 20 percent reduction in the acetylation of isoniazid, especially in patients who are rapid acetylators; INH serum levels, half lives and excretions in fast acetylators still remain half of the levels seen in slow acetylators with or without p-aminosalicylic acid. The effect is dose related and, while it has not been studied with the current delayed release preparation, the lower serum levels with this preparation will result in a reduced effect on the acetylation of INH.
Aminosalicylic acid has previously been reported to block the absorption of rifampin. A subsequent report has shown that this blockade was due to an excipient not included in PASER granules. Oral administration of a solution containing both aminosalicylic acid and rifampin showed full absorption of each product.
As a result of competition, Vitamin B_{12} absorption has been reduced 55% by 5 grams of aminosalicylic acid with clinically significant erythrocyte abnormalities developing after depletion; patients on therapy of more than one month should be considered for maintenance B_{12}.
A malabsorption syndrome can develop in patients on aminosalicylic acid but is usually not complete. The complete syndrome includes steatorrhea, an abnormal small bowel pattern on x-ray, villus atrophy, depressed cholesterol, reduced D-xylose and iron absorption. Triglyceride absorption always is normal.
In one literature report 8 hours after the last dosage of aminosalicylic acid at 2 gm qid serum digoxin levels were reduced 40% in two of ten patients but not changed in the remaining eight.

(5) Carcinogenesis, mutagenesis, impairment of fertility:
Sodium aminosalicylate produced an occipital bone defect, probably with a dose response, when administered to ten pregnant Wistar rats at five doses from 3.85 to 385 mg/kg from days 6 to 14. There were no significant changes from controls in any group in corpora lutea, early resorptions, total resorptions, fetal death, litter size, or hematomas. For all except the 77 mg/kg group, fetal weights were significantly greater than controls. Chinchilla rabbits on 5 mg/kg from days 7 to 14 did not show any significant differences as compared to controls for the same parameters studied.
Sodium aminosalicylic acid was not mutagenic in Ames tester strain TA 100. In human lymphocyte cultures in-vitro clastogenic effects of achromatic, chromatid, isochromatic breaks or chromatid translocations were not seen at 153 or 600 μg/mL. At 1500 and 3000 μg/mL there was a dose related increase in chromatid aberrations.
Patients on isoniazid and aminosalicylic acid have been reported to have an increased number of chromosomal aberrations as compared to controls.

(6) Pregnancy: Pregnancy Category C:
Aminosalicylic acid has been reported to produce occipital malformations in rats when given at doses within the human dose range. Although there probably is a dose response, the frequency of abnormalities was comparable to controls at the highest level tested (two times the human dosage). When administered to rabbits at 5 mg/kg, throughout all three trimesters, no teratologic or embryocidal effects were seen. Literature reports on aminosalicylic acid in pregnant women always report coadministration of other medications.

Because there are no adequate and well controlled studies of aminosalicylic acid in humans, PASER granules should be given to a pregnant woman only if clearly needed.

(8) Nursing mothers:
After administration of a different preparation of aminosalicylic acid to one patient, the maximum concentration in the milk was 1 μg/mL at 3 hours with a half-life of 2.5 hours; the maximum maternal plasma concentration was 70 μg/mL at two hours.

ADVERSE EFFECTS
The most common side effect is gastrointestinal intolerance manifested by nausea, vomiting, diarrhea, and abdominal pain.
Hypersensitivity reactions: Fever, skin eruptions of various types, including exfoliative dermatitis, infectious mononucleosis-like, or lymphoma-like syndrome, leucopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, jaundice, hepatitis, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Leoffler's syndrome, vasculitis and a reduction in prothrombin.
Crystalluria may be prevented by the maintenance of urine at a neutral or an alkaline pH.

OVERDOSAGE
Overdosage has not been reported.

DOSAGE AND ADMINISTRATION
PASER granules should be administered with other drugs to which the organism is known or expected to be susceptible. It is most commonly administered to patients with Multi-drug Resistant TB (MDR-TB) or in other situations in which therapy with isoniazid or rifampin is not possible due to a combination of resistance and/or intolerance. The adult dosage of four grams (one packet) three times per day or correspondingly smaller doses in children should be given by sprinkling on apple sauce or yogurt or by swirling in the glass to suspend the granules in an acidic drink such as tomato or orange juice.
DO NOT USE if packet is swollen or the granules have lost their tan color, turning dark brown or purple.

HOW SUPPLIED
Carton of 30 PASER packets (NDC 49938-107-04).
Each packet contains four grams aminosalicylic acid.
PASER granules are supplied in packets containing 4 grams of aminosalicylic acid for administration three times a day by suspension in an acidic drink or food with a pH less than 5. Examples include apple sauce, yogurt, tomato or orange juice.
Distributors and Pharmacists: Store below 59°F (15°C) (in a refrigerator or freezer).
Patients are urged to store PASER in a refrigerator or freezer. PASER packets may be stored at room temperature for short periods of time.
AVOID EXCESSIVE HEAT. DO NOT USE if packet is swollen or the granules have lost their tan color, turning dark brown or purple.
JACOBUS PHARMACEUTICAL CO. INC.
P.O. Box 5290
Princeton, NJ 08540
2A JULY, 1996

PRINCIPAL DISPLAY PANEL
Principal Display Panel – 4g Carton Label
NDC 49938-107-04
PASER® Aminosalicylic Acid
Delayed-release Granules
4 Grams
30 Unit Dose Packets
STORE BELOW 59°F (15°C)
ALTERNATIVELY STORE IN A
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AVOID EXCESSIVE HEAT
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DIRECTIONS FOR USE:

The granules should be taken without chewing by sprinkling on an acidic food (apple sauce or yogurt) or swirled with a juice (Examples: orange, tomato, apple) listed in accompanying literature. The coating will last at least 2 hours.

USUAL DOSAGE

Read accompanying literature.

WARNING:

DO NOT USE IF packets are swollen or the granules have lost their tan color and are dark brown or purple. Inform your pharmacist or physician immediately and return medication.

STORE BELOW 59°F (15°C), ALTERNATIVELY STORE IN A REFRIGERATOR OR FREEZER, AVOID EXCESSIVE HEAT

CONTROL NUMBER:
EXPIRES:

MADE IN USA 2A0796

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